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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,556	07/26/2003	Jeffrey A. Ledbetter	910180.401C2	3297

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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,556	LEDBETTER ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/22/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *94-96 and 110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *110* is/are allowed.

6)☒ Claim(s) *94-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 94-96 and 110 are all the pending claims for this application.

2. Claims 94-96 were amended in the Response of 7/22/09.

3. Claims 94-96 and 110 are all the pending claims under examination.

4. The finality of the Office Action is withdrawn in view of the new grounds for rejection.

Withdrawal of Objections

Specification/ New Matter

5. The objection to the amendment filed 2/18/09 under 35 U.S.C. 132(a) because it introduces new matter into the disclosure is withdrawn.

The examiner acknowledges Applicants amended specification to cross-reference related applications, but which have otherwise been disavowed in the priority claim for this application by Applicants statements and the revised ADS in the response of 2/18/09.

Additionally, it is noted that the phrase "incorporation by reference" appeared in Cross-Reference section in the original filed specification of 7/26/03 for the relevant priority documents.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

6. The rejection of Claims 94-96 in lacking antecedent basis for the limitation "said binding domain polypeptide" in element i) of Claims 94-96 withdrawn in view of the amendment to bring the claims into proper antecedency.

Claim Rejections - 35 USC § 103

7. The rejection of Claims 94-96 under 35 U.S.C. 103(a) as being obvious over Ledbetter et al. (US 20030118592; published 6/26/03; cited in the PTO 892 form of 11/26/08) as evidenced by Pluckthun et al. (USPN 6,815,540; published 11/9/2004; filed 1/15/1999; hereinafter referred to as "Pluckthun"; cited in the PTO 892 form of 12/8/06) in view of Welschof et al. (Human Immunol. 60:282-290 (1990)) is withdrawn.

Applicants have excluded the Ledbetter reference based on common ownership at the time the instant invention was made and have provided the required statement on p. 6, ¶4 of the Response of 7/22/09. The secondary references alone or combined do not support or sustain the rejection, and therefore, the secondary references also fall.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

8. Claims 94-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a G28-1 scfv-Ig comprising both a VH and VL recognizing CD37 and obtained from the G28-1 antibody, does not reasonably provide enablement for a G28-1 scfv-Ig having only the single VH domain and recognizing CD37. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 94-96 are interpreted as being drawn to a fusion protein comprising a binding domain comprising the G28-1 scfv where amino acid residue 11 of the VH chain is serine, where the binding domain is attached to an altered w-t IgG1 hinge comprising C-C-P) and being altered to as to be (S-S-S) where the hinge is attached to an N-terminally truncated Ig heavy chain constant region comprising CH2 and CH3 of IgG1 (Claim 94), and Claim 95 is the same as Claim 94 except the altered hinge is (C-S-S),

and Claim 96 is the same as Claim 94 or 95 except the altered hinge is (S-S-P). the claims are examined with respect to the enabling disclosure for fusion proteins comprising a single VH domain.

The relative skill in the art required to make and use the invention is a molecular immunologist.

Disclosure in the Specification

The specification teaches antibodies for CD37 comprising full length antibodies, fragments and scfv including G28-1. the specification does not enable a fusion protein comprising a single variable domain (VH) obtained from the G28-1 antibody being linked by the altered hinge to the truncated heavy chain constant region from IgG1 comprising CH2 and CH3. The specification does not enable any fusion molecules that are scFV that have only one VH of a heavy chain.

The claims are not commensurate in scope with the enablement provided in the specification. The specification does not support the broad scope of the claims which encompass an anti-CD37 (G28-1) antibody single heavy chain variable domain because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance;

The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; and

The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimedf usion protein in manner reasonably correlated with the scope of the claims broadly including a single heavy chain variable domain that binds CD37. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Applicants' specification is deficient in its disclosure of the full scope of the claimed invention and does not provide sufficient guidance for even the most skilled artisan to practice making and using the breadth of fusion antibodies encompassed by the claims absent undue experimentation.

Prior Art Status: Binding specificity for single domain antibodies is unpredictable

The single domain antibodies taught in WO 2004/003019 (Domantis) and Ward et al. (Nature 341:544-546 (1989)) appear to be examples of single domain antibodies generated against a limited number of antigens that have been shown to retain antigen binding specificity. However, Ward teaches and cautions:

"Separated heavy and light chains have previously been identified with antigen or hapten binding activities although the affinities were poor, with no evidence for binding by single chains rather than dimers" (p. 544, Col. 2) and

"However, VH domains are relatively sticky, presumably due to the exposed hydrophobic surface normally capped by the Vκ and Vλ domains" (p. 546, Col. 1).

By and large, the art recognizes that single domain antibodies do not provide the sufficient contact sites for antigen binding or at the very least the molecules tend to be less soluble and otherwise form aggregates.

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Unpredictability/ Undue Experimentation

The specification provides no direction or guidance regarding how to produce the genus of chimeric antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 94-96 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 8, 10, 11, 16, 18, 20, and 21 of copending Application No. 12/371,467 (not yet published). Although the conflicting claims are not identical, they are not patentably distinct from each other because the fusion protein comprising the G28-1 scFv-Ig with an altered IgG1 hinge regions of the instant claims is not nearly novel or nonobvious over '467.

The claims of '467 are as follows:

> 1. A fusion protein comprising from amino-terminus to carboxy-terminus: (i) an immunoglobulin binding domain polypeptide capable of binding a target molecule, wherein the binding domain polypeptide comprises a heavy chain variable region having a mutated amino acid residue; (ii) an altered immunoglobulin hinge polypeptide comprising a cysteine and a proline substituted for a different amino acid; and (iii) an amino-terminally truncated immunoglobulin heavy chain constant region polypeptide.
>
> 3. The fusion protein of claim 1 wherein the heavy chain variable region has an amino acid substitution at position 11 that is serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine,

arginine, or histidine.

4. The fusion protein of claim 1 wherein the binding domain is a single chain Fv polypeptide.

8. The fusion protein of claim 4 wherein the single chain Fv is from...G28-1,...

10. The fusion protein of claim 1 wherein the amino-terminally truncated immunoglobulin heavy chain constant region polypeptide comprises a human CH2 constant region polypeptide attached to a human CH3 constant region polypeptide.

11. The fusion protein of claim 10 wherein the CH2 and CH3 constant region polypeptides are an...IgG1, ...constant region polypeptides.

16. The fusion protein of claim 1 wherein the altered immunoglobulin hinge polypeptide comprises an altered human IgG1...hinge region.

18. The fusion protein of claim 1 wherein the altered immunoglobulin hinge polypeptide comprises an altered wild type IgG 1 immunoglobulin hinge region, wherein the wild type IgG1 hinge region comprises first, second, and third cysteine residues, and a proline, wherein the first cysteine reside is N-terminal to the second cysteine, the second cysteine is N- terminal to the third cysteine, and the third cysteine is N-terminal to the proline residue, and wherein the altered immunoglobulin hinge polypeptide has only the third cysteine or has only the first and third cysteines of a wild type IgG1 hinge region.

20. The fusion protein of claim 1 wherein the altered immunoglobulin hinge polypeptide comprises an altered wild type IgG1 immunoglobulin hinge region, wherein (i) the wild type IgG1 hinge region comprises first, second, and third cysteine residues, and a proline, wherein the first cysteine reside is N-terminal to the second cysteine, the second cysteine is N- terminal to the third cysteine, and the third cysteine is N-terminal to the proline residue, (ii) the proline N-terminal to the third cysteine in the

hinge is substituted, and (iii) (a) the second cysteine is substituted; (b) the third cysteine is substituted; (c) the first and second cysteines are substituted; (d) the first and third cysteines are substituted; or (e) the second and third cysteines are substituted.

21. The fusion protein of claim 20 wherein the substitution is with a serine,...

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

10. Claim 110 is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner
Art Unit 1643